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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/230,463	07/26/1999	DAVID WYNICK	23016.0002	4323

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EXAMINER	
GUCKER, STEPHEN	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/230,463	WYNICK, DAVID	
	Examiner	Art Unit	
	Stephen Gucker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/13/06 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

4. Claims 27-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. For claims 33 and 43, the specification as filed does not describe galanin agonists that comprise, by the specific number of twelve amino acids, galanin agonists that comprise 12 N-terminal amino acids of galanin. It is noted by the Examiner that the description of WO92/20709 by the instant specification on page 1 is technically incorrect. WO92/20709 appears to the Examiner to be completely silent on the matter of 12 N-terminal amino acid fragments of galanin as being galanin agonists. In fact, this WO92/20709 does not appear to disclose any

teachings on galanin agonists, but only galanin antagonists. This is a new matter rejection.

Furthermore, the specification does not describe methods of treatment comprising administering galanin agonists whereby regeneration into the distal nerve is increased (claims 27-29, 33-39, and 43-45) or the galanin agonist is effective to increase the rate of regeneration of sensory nerve axons (claims 30-36 and 40-45) or the galanin agonist is effective to stimulate regeneration of sensory nerve axons (claims 27-29, 33-39, and 43-45). What the specification does describe is, on page 5, lines 4-7, "The mammal or tissue, cells and cell lines of the invention may be used in an assay to study one or more biological effects of galanin. The biological effect may be selected from...growth or the repair of nerve damage." First, the specification is describing assay methods, not treatment methods. Second, the mammal, tissue, cell or cell lines that the specification is referring to are all from sources that do not express galanin peptide due to genetic engineering, while the instant claims describe treating neuropathy in non-genetically engineered subjects, i.e. "wild-type." Furthermore, the specification on pages 10-11 describes observations of sensory nerve regeneration in a genetically engineered mouse model that does not express galanin peptide (i.e. a "knock-out" mouse). There is no written description of treating this mouse by administering galanin agonists. Finally, page 12, lines 9-11 of the specification describe the use of a galanin agonist in the treatment of sensory neuropathy. There is no written description concerning said galanin agonist whereby regeneration into the distal nerve is increased (claims 27-29, 33-39, and 43-45) or the galanin agonist is effective to increase the rate of regeneration

of sensory nerve axons (claims 30-36 and 40-45) or the galanin agonist is effective to stimulate regeneration of sensory nerve axons (claims 27-29, 33-39, and 43-45). This is a new matter rejection.

5. The following is a quotation of the sixth paragraph of 35 U.S.C. 112:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Claims 27-32 are being examined under 35 U.S.C. 112, sixth paragraph, as they have invoked examination under 35 U.S.C. 112, sixth paragraph, as they are in compliance with the "three prong" test. Specifically, claims 27-32 recite the "means for" phrase, the "means for" phrase is modified by functional language, and the "means for" phrase was not modified by structure, material or acts for achieving the specified function. See MPEP § 2181-2185 (Rev 3, August 2005). However, claims 33-36 fail the "third prong" by reciting limitations that modify the structure of the galanin agonist recited in the independent claims, and therefore dependent claims 33-36 will not be examined under 35 U.S.C. 112, sixth paragraph.

6. Claims 27-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising the use of galanin or N-terminal fragments of galanin that are galanin agonists, does not reasonably provide enablement for galanin agonists or fragments in general for reasons of record and the following. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

commensurate in scope with these claims. The disclosure teaches that galanin is a 29 amino acid neuropeptide and that the N-terminal portion of galanin is highly conserved between species. It is also disclosed that the prior art teaches that N-terminal fragments of galanin augment the effect of morphine, and this augmentation was known in the art as an agonistic effect. Furthermore, Bartfai et al. (*TiPS, Vol. 13*, page 312, 1992, reference D, PTO-1449 filed 5/24/99) discloses that the smallest N-terminal fragment of galanin that has agonist activity is the N-terminal amino acid residues from amino acid residue or position 1 to amino acid residue or position 12, i.e. galanin$_{1-12}$. Accordingly, the specification does not provide an adequate written description, examples, or guidance to fully support the use of a galanin agonist or agonist fragments in general that are not N-terminal fragments for the following reasons. A galanin agonist is any compound that physiologically functions like galanin, *regardless of its structure*. The instant specification states that "the term 'galanin' embraces all known galanins including, for example, human, rat, murine and porcine galanin and <u>also analogues of galanin having the biological activity of galanin</u>" (page 4, underlining mine). The Examiner is relying on this teaching to determine the scope of the means plus function language recited in the claims. Since "analogues of galanin having the biological activity of galanin" is the clearest teaching presented in the specification to almost identically recite the means plus function claim language, claims 27-32 are of undue scope for the following reasons. The only known galanin agonists of record at the time of the effective filing date of the instant application (7/24/96) were galanin itself and certain N-terminal fragments of galanin, the shortest sequence being galanin$_{1-12}$. The phrase "galanin

agonist" includes any compounds, including non-peptides, that function like galanin. The instant methods encompass the use of any molecule that acts like galanin ("biological activity of galanin"), therefore the limitation is functional rather than structural. The scope of the compounds used in the instant claims is therefore very broad, because the breadth is unfettered by any structural limitations. But, the relationship between function and structure for biological peptides is poorly understood. Even minor amino acid changes in a small peptide can bring about radical changes in function (see Rudinger, page 3 and Figure 1.2). Rudinger also states that "the significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (Rudinger, page 6). The breadth of the instant claims captures the use of any galanin agonist that is not envisioned or adequately supported by the specification, and even though the skill of the practitioner is high (Ph.D., M.D.), the full reasonable enablement of the claims, as Rudinger states, requires "painstaking experimental study," which is clearly beyond routine experimentation with no reasonable expectation of success, even for the skilled practitioner. In summation, and for the reasons given above, the specification does not provide an adequate description, any working examples, or sufficient guidance as to what compounds can be used in the methods as enabled galanin agonists, other than galanin and N-terminal fragments of galanin that are galanin agonists.

Applicant's arguments and declaration filed 11/9/05 have been fully considered but they are not persuasive because the arguments and declaration are in agreement

with the scope rejection of record. The rejection of record limits the scope of the claim to methods comprising the use of "galanin and N-terminal fragments of galanin that are galanin agonists." Applicant argues, essentially, that there are 6 known galanin agonists (other than galanin itself) in existence as of the instant effective filing date of 1996, made from the N-terminal region of galanin, which the record has already established to be highly conserved (i.e. similar sequence of amino acids) in both chemical structure and function between different species of animals. Because neither Applicant's arguments or the declaration of Dickenson filed 11/9/05 provide any evidence or valid scientific support or reasoning for galanin agonists that do not comprise at least the N-terminal region of galanin, the rejection is maintained. Applicant's arguments drawn to screening assays to discover unknown galanin agonists are unconvincing as the screening assays have been in use for over ten years (effective date of filing), and the only galanin agonists of record comprise the N-terminal region of galanin, so screening assays for galanin agonists do not place the invention into the hands of the public without undue experimentation when the invention is, in fact, a method of treatment using galanin agonists, and such galanin agonists as a broad functional genus are not scientifically predictable in terms of what their chemical structure comprises in general, after over ten years of research work, other than the N-terminal fragments or region of the galanin peptide itself. Since Applicant did not offer any supported opposing viewpoint to the published work of Rudinger, Applicant's allegations that Rudinger is too old a reference is also unconvincing. Rudinger's observations concerning the unpredictability of peptide structure given only the peptide's function remain unrebutted,

and "biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (Rudinger, page 6).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 27-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 45 is vague and indefinite as it is not clear how an N-terminal fragment of galanin peptide can actually be the galanin peptide itself. Using normal scientific terminology, a fragment of a peptide is at least one amino acid residue shorter than the peptide itself.

Claims 27-45 are also vague and indefinite because the preamble of the claims recites "a method for the treatment of peripheral sensory neuropathy," but the body of the claims recite "comprising administering to the subject an amount of a galanin agonist effective to stimulate regeneration of sensory nerve axons, whereby regeneration into the distal nerve is increased" (claims 27 and 37) or "comprising administering to the subject an amount of a galanin agonist effective to increase the rate of regeneration of sensory nerve axons" (claims 30 and 40). Therefore, the body of the claims do not relate back to the preamble of the claims. While the preamble recites a method for the treatment of peripheral sensory neuropathy, the body recites a method to stimulate regeneration of sensory nerve axons or to increase the rate of regeneration of sensory nerve axons. The relationship between the preamble of the process claims and the body of the process claims is vague and unclear.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 27 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Gao (US 6,429,191 B1, effective filing date of provisional application 60/044,407, filed 1/5/06). Gao discloses methods for treating peripheral sensory neuropathy by administering neurotrophins (column 2, line 63 to column 3, line 62; column 5, lines 41-50; column 6, lines 37-51; column 7, lines 15-27, lines 36-46, and line 54; column 9, lines 20-53; column 12, lines 33-46 (explicitly discloses regenerating axons); column 27, lines 15-22 (discloses neurotrophins elicit neurite outgrowth from sensory neurons); column 32, lines 13-26 (explicitly discloses treating neuronal degeneration, damage, and loss, also know as neuropathies); and column 46, lines 9-20 (discloses that cisplatin neurotoxicity results in a peripheral sensory neuropathy, and the aforementioned cited portions of this patent disclose that neurotrophins are an effective

treatment). Neurotrophins are being interpreted by the Examiner as being analogues of galanin having the biological activity of galanin under 35 U.S.C. 112, sixth paragraph, because "analogues of galanin" are described in the specification as simply "having the biological activity of galanin," and the new instant claims assert that the biological activity of galanin is to promote axonal regeneration, which is also a biological activity of the neurotrophins in the prior art. Due to the indefinite nature of claims 27 and 30 as noted in the 35 U.S.C. 112, second paragraph rejection set forth above, Gao is being held as prior art for anticipating the instant claims' preamble of a method of treating peripheral sensory neuropathy by administering a galanin agonist (analogue of galanin having the biological activity of galanin), and the neurotrophins disclosed by Gao have the sensory axonal regenerating capability as recited in the instant claims.

The Zigmond declaration filed 7/1/04 has been fully considered but is not persuasive because the declaration is drawn to limitations not recited in the claim. The claim is not limited to peripheral administration of galanin, nor does the claim limitation exclude the use of galanin to treat peripheral nerve damage that concomitantly produces neuropathic pain. Furthermore, there are no limitations in the claim as to what comprises "nerve regeneration" while Applicant's arguments and declaration are drawn to observable, complete and full regeneration. Nerve regeneration as recited in the instant claim encompasses the preliminary beginnings of regeneration up to and including its full completion and expression, and nothing persuasive is provided by Applicant's arguments or declaration that nerve regeneration does not begin within a

few minutes or hours of administering galanin, absent any evidence of record to the contrary.

11. Claims 27, 30-34, 36-37, 40-43, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. ("Luo") in view of Zhang et al. ("Zhang") and further in view of Villar et al. Luo describes methods where galanin is administered to treat spinal cord hyperexcitability following sciatic nerve section (abstract and pages 162-163) which produces peripheral neuropathy as taught by the instant Application (pages 11-12 of the instant specification, where an example of sciatic nerve axotomy (otherwise known as section) and upregulation of galanin is disclosed as support for the idea that galanin agonists can be administered to treat peripheral sensory neuropathy). Luo does not teach chronic or long-term administration of galanin following sciatic nerve section. Zhang does suggest chronic or long-term administration of galanin agonists to treat peripheral nerve lesions, which are a form of peripheral sensory neuropathy. Zhang discloses that the findings in rat concerning galanin are valid and applicable in primates as well.

> "The main reason underlying our experiments was to explore whether the peptide galanin is upregulated in primates as it is in rats, since we have proposed that galanin may represent an endogenous analgesics compound activated after peripheral nerve lesions. Consequently, galanin agonists should represent new pharmacological tools to suppress chronic pain. The present findings show that, since some of these mechanisms also operate in monkey, this hypothesis is valid also for primates and provide a further impetus to test galanin or galanin agonists in humans" (page 375 of Zhang).

Zhang does not carry out the experiments that he explicitly suggests, nor does Zhang propose a specific time frame in regards to chronic pain. Villar does disclose specific time frames for the upregulation of a galanin agonist (galanin itself) that occurs during

peripheral sensory neuropathy. Specifically, Villar teaches that galanin levels rise about 120-fold after 3 and 14 days after transection and can remain higher than normal 2 to 6 months after transection (abstract and page 589). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use galanin as a treatment following peripheral neuropathy as taught by Luo and/or Zhang, for therapeutic purposes, because Zhang explicitly makes the suggestion to do so, and Villar provides guidance as to a therapeutically useful specific time frame that peripheral nerve lesions induce an upregulation of a galanin agonist (galanin itself) on the order of 3-14 days post-injury for heavy upregulation, and 2-6 months post-injury for at least some upregulation. Note that Zhang, in the context of peripheral nerve lesions (i.e. damage), makes the explicit suggestion that "galanin agonists should represent new pharmacological tools to suppress chronic pain" (underlining mine). Chronic pain in humans clearly implies the repeated use of galanin over a period of time that spans weeks, months, even years (the Zhang study was performed over a period of two weeks time, Villar up to 6 months). Therefore, the references render *prima facie* obvious a method to use galanin agonists to treat peripheral neuropathy, and to extend the use of galanin agonists in humans to treat chronic pain from peripheral nerve lesions, as suggested by Zhang. The repeated, chronic use of galanin agonists in humans as suggested by the prior art to treat chronic pain would result in the galanin agonists promoting nerve regeneration, as required by the limitations of the instant claims. The promotion of nerve regeneration occurring by the chronic use of galanin to treat chronic pain is also supported by Applicant's arguments and affidavits that are directed to nerve

regeneration occurring with the use of galanin over a period of time such as 24 hours and beyond, as measured by such phenomenon as retrograde axonal transport of galanin.

Applicant's arguments filed 11/9/05 have been fully considered but they are not persuasive because Applicant argues that many pain-treating compounds do not promote nerve regeneration. However, the Zhang reference discloses the same evidentiary support for the instant invention as the instant specification does: namely, that following peripheral nerve axotomy, levels of galanin increase in response to the lesion. Given that the prior art reference and the instant disclosure teach the identical finding, Applicant's arguments are unconvincing because they encompass compounds such as aspirin, while the prior art reference is clearly dead on point because it provides motivation to use galanin itself as a method of chronic treatment for peripheral neuropathy.

Applicant's arguments filed 9/13/06 have been fully considered but they are not persuasive because Applicant argues that Luo deal exclusively with neuropathic pain behavior, not with peripheral nerve damage such as peripheral sensory neuropathy--- peripheral nerve damage is in no way synonymous with chronic neuropathic pain, Applicant states. This argument is not persuasive because Luo describes methods where galanin is administered following sciatic nerve section (abstract and pages 162-163) which produces peripheral neuropathy as taught by the instant Application (pages 11-12 of the instant specification). Applicant further argues limitations, such as central versus peripheral administration of galanin, which are not recited in the instant claims.

Applicant further argues that Zhang is limited to teachings dealing with chronic neuropathic pain which is in no way synonymous with the treatment of peripheral nerve damage. This argument is not persuasive because Zhang states "that galanin may represent an endogenous analgesics compound activated after peripheral nerve lesions" (underlining mine), which is synonymous with peripheral nerve damage. Finally, Applicant asserts that the present inventor found the surprising result that nerve regeneration is stimulated by galanin in a dose-dependent manner. This is not technically correct. The present inventor found that in a knock-out transgenic mouse that could not express galanin, regeneration of sensory peripheral axons was impaired as compared to normal mice. The inventor never administered galanin in any treatment of a normal or knock-out mouse to demonstrate the surprising result that galanin stimulated nerve regeneration in a dose-dependent manner. Regeneration of sensory peripheral axons is not an unexpected result (see Villar, pages 599-600, and Zhang, page 373).

12. No claim is allowed.

13. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technical Center 1600 general number which is (571) 272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (571) 272-0883. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Janet Andres, can be reached at (571) 272-0867. The fax phone number for this Group is currently (571)-273-8300.

SG

Stephen Gucker

November 9, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER